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Evaluation of real-time data obtained from gravimetric preparation of antineoplastic agents shows medication errors with possible critical therapeutic impact: Results of a large-scale, multicentre, multinational, retrospective study

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Summary

What is known and objective: Medication errors are a significant cause of morbidity and mortality especially with antineoplastic drugs, owing to their narrow therapeutic index. Gravimetric workflow software systems have the potential to reduce volumetric errors during intravenous antineoplastic drug preparation which may occur when verification is reliant on visual inspection. Our aim was to detect medication errors with possible critical therapeutic impact as determined by the rate of prevented medication errors in chemotherapy compounding after implementation of gravimetric measurement.

Design: A large-scale, retrospective analysis of data was carried out, related to medication errors identified during preparation of antineoplastic drugs in 10 pharmacy services ("centres") in five European countries following the introduction of an intravenous workflow software gravimetric system. Errors were defined as errors in dose volumes outside tolerance levels, identified during weighing stages of preparation of chemotherapy solutions which would not otherwise have been detected by conventional visual inspection.

Key results: The gravimetric system detected that 7.89% of the 759 060 doses of antineoplastic drugs prepared at participating centres between July 2011 and October 2015 had error levels outside the accepted tolerance range set by individual centres, and prevented these doses from reaching patients. The proportion of antineoplastic preparations with deviations >10% ranged from 0.49% to 5.04% across sites, with a mean of 2.25%. The proportion of preparations with deviations >20% ranged from 0.21% to 1.27% across sites, with a mean of 0.71%. There was considerable variation in error levels for different antineoplastic agents.

What is new and conclusion: Introduction of a gravimetric preparation system for antineoplastic agents detected and prevented dosing errors which would not have been recognized with traditional methods and could have resulted in toxicity or suboptimal therapeutic outcomes for patients undergoing anticancer treatment.

This report employed the SQUIRE publication guidelines for reporting healthcare quality improvement research. [Ogrinc G, Davies L, Goodman D, et al. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf* Published Online First: 14 September 2015. doi: 10.1136/bmjqs2015-004411].

KEYWORDS
antineoplastic agents, gravimetric IV workflow software system, medication errors, preparation, safety

1 | WHAT IS KNOWN AND OBJECTIVE

Medication errors are a significant cause of morbidity and mortality and may occur at any stage during prescription, preparation, dispensing or administration of drugs. Errors with antineoplastic drugs are particularly hazardous owing to their mechanism of action and narrow therapeutic index (TI) and the frequently poor performance status of cancer patients. In a retrospective analysis of mortality associated with medication errors, antineoplastic drugs were the second most common cause of involvement in death.[1]

National and international guidelines have proposed methods of minimizing and preventing medication errors in the clinic, pharmacy and patient's home.[2-4] In the pharmacy, information technology and automated workflow software systems have the potential to verify and prevent preparation and dispensing errors, such as miscalculation of drug concentration and incorrect use of diluent.

Traditionally, preparation of intravenous (IV) antineoplastic drugs has depended on the volumetric approach whereby a volume of a solution of a prescribed agent is withdrawn from the original vial (with or without prior addition of a diluent) and either administered in the original concentration or further diluted in a parenteral infusion solution. Checking for errors depends on real-time visual inspection or retrospective review of digital images.

The introduction of the gravimetric approach to preparation of IV agents supported by expert software aims to reduce the potential for errors associated with visual inspection. At each stage of drug preparation, measured solutions are weighed on an electronic balance and results related to the density of the components were stored in the system's database. In this way, the accuracy of the prepared volume is checked to ensure it falls within acceptable margins for error. Figure 1 provides a visual comparison of the volumetric (with syringes being a main driver of inaccuracy [Figure 2][5]) and gravimetric methods of preparation of prescribed doses.

European guidance supports the use of the computer-assisted gravimetric approach for preparation of individualized ready-to-use cytostatic solutions,[4] and systems have been introduced in many pharmacies in Europe. However, little research has been reported on the evaluation of the extent and prevalence of medication errors and their potential for prevention by gravimetric systems. Results of a recent US single-centre study using gravimetric IV workflow software system showed an error detection rate of 7% in 15 843 doses prepared in an oncology ambulatory care pharmacy, with 71% detected during gravimetric weighing.[6]

To help improve current knowledge surrounding medication errors arising from preparation of oncology medicines, and to provide a reliable basis for the assessment of possible clinical effects, we carried out a large-scale, retrospective analysis of data. This related to medication errors identified during preparation of antineoplastic drugs at European pharmacies serving oncology services following the introduction of an IV workflow software gravimetric system (BD Cato™, Becton, Dickinson and Company, Franklin Lakes, NJ, USA). The oncology setting was chosen due to the narrow margin of safety for many chemotherapy solutions and the high volume of IV medicines specifically compounded for individual patients in dedicated units.

2 | METHODS

Medication errors were defined as errors in dose volumes, outside tolerance levels, identified during weighing stages of preparation of chemotherapy solutions which would not otherwise have been detected.

The study's primary outcome was the number and percentage of doses that failed to stay within each centre's preset tolerance limits for their gravimetric software systems, for dosing errors that satisfied local needs (Table 1). Secondary outcomes included number and proportion of doses not prepared correctly at the first attempt, as well as number and percentage of preparations with deviations >10% and >20%, either above or below target dose. The study also investigated whether medication errors were more frequent with some types of IV chemotherapy.

A total of 759 060 unique preparations carried out by 245 technicians working in 10 centres in five European countries (Austria, Czech Republic, Denmark, Germany and Switzerland) were included in this evaluation (Recruitment and Evaluation Process see Online appendix A1).

3 | RESULTS

Error tolerance levels set by centres varied from 2.5% to 6%, and the maximum difference in preparation tolerance was 3.5%. However, extended tolerances of up to 30% (range 3.1% to 30%) were found for medications that are formulated in a manner difficult to stay within normal limits for preparation (Table 1). Medicines most frequently assigned extended tolerances included bortezomib, vincristine, methotrexate and cytarabine. Tolerance ranges for these and other medicines were highly variable; for example, the extended tolerance for bortezomib at centre 6 was 3.1-3.98, compared to 12.11-20.63 at centre 9.

The proportion of antineoplastic drug samples that were outside centre tolerance levels ranged from 5.65% to 16.37% with an overall proportion of 7.89% (Table 1). The mean error rate across centres

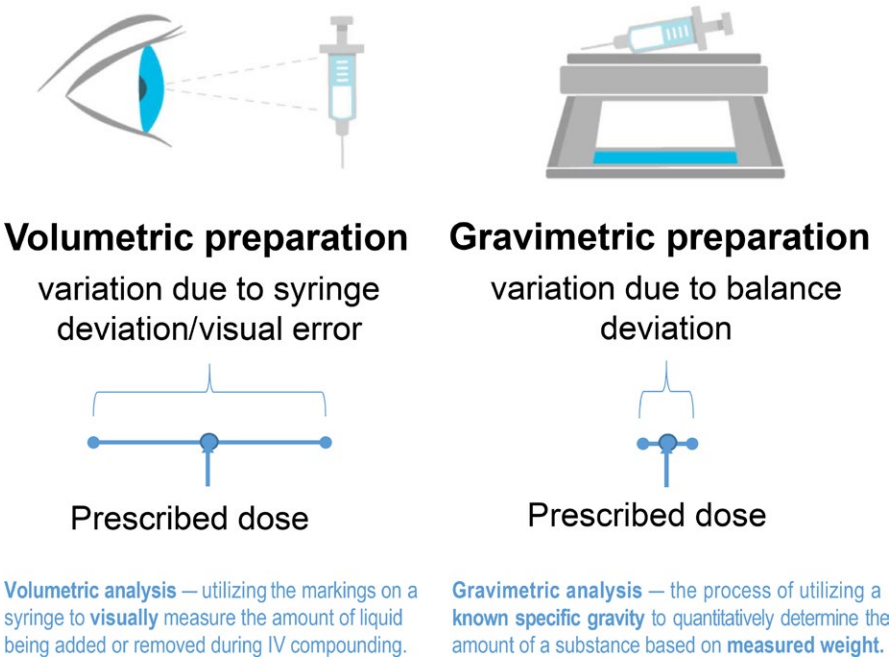

FIGURE 1 Volumetric versus gravimetric preparation

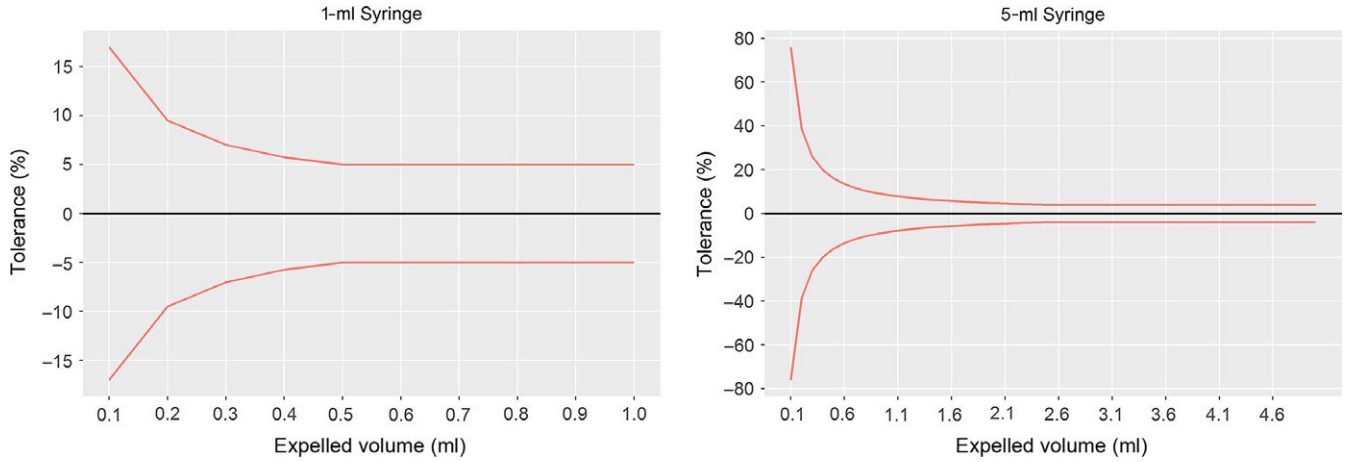

FIGURE 2 Tolerance of 1- and 5-mL syringes (<5 mL nominal capacity [NC]: allowed tolerance of ±5% on expelled volumes [EVs] that are equal to or greater than half the NC. For EVs that are less than half the NC, the tolerance obtained is ±1.5% of the NC +2% of the EV. ≥5 mL NC: tolerance is reduced to ±4% on EVs that are equal to or greater than half the NC, and for EVs that are less than half the NC, the tolerance is obtained as ±1.5% of the NC +1% of the EV)[5]

(adjusting for unequal number of preparations at different centres) was 10.44%. It might have been expected that centres with the lowest tolerance for error would have the highest error rates but, in our study, the centre with the lowest number of preparations out of tolerance (OOT) (centre 3) had one of the lowest tolerance levels. In contrast, the centre with the highest percentage of OOT preparations (centre 7) had a relatively high tolerance threshold (5%).

Excluding preparations with extended tolerances >10%, the proportion of antineoplastic preparations with deviations >10% of target dose ranged from 0.49% to 5.04% across sites, with a mean of 2.25%. The proportion of preparations with deviations >20% of target dose ranged from 0.21% to 1.27% across sites, with a mean of 0.71% (Table 2).

The centre with the highest proportion of OOT preparations (centre 7: 16.37%) also showed the poorest performance with deviations >10% (5.04%) and >20% (1.1%) (Tables 1 and 2).

Analysis of antineoplastic preparations compounded correctly at first attempt showed that 9.5% of doses were not effectively prepared "at the first attempt" (range 6.6% to 19%) (Table 1). The average proportion of preparations requiring more than one attempt across hospitals (adjusting for unequal number of preparations at different centres) was 13.77%. The need for repeat preparation was most common at centres with the highest proportion of OOT preparations.

Further analyses show that antineoplastic preparations were more likely to be OOT when very small amounts of drug were being prepared (Figure 3) and that, at most centres, levels of

TABLE 1 Error tolerance level (%), number of preparations out of tolerance (%), number of preparations not prepared correctly at first attempt (%) and range of extended tolerance (%) for centres in the study

Centre	Tolerance for withdrawal (%)	Out of tolerance (%)	Not at first attempt (%)	Range of extended tolerance
Centre 1	4.8	11.23	18.4	4.82-10
Centre 2	5	8.71	16.2	5.04-25.78
Centre 3	3	5.65	8.1	
Centre 4	6	6.14	6.6	6-25.26
Centre 5	3	12.07	13.6	3.54-30
Centre 6	3	14.36	18.8	3.1-20.81
Centre 7	5	16.37	19	10.17-21.45
Centre 8	4	7.74	11.8	4.01-14.51
Centre 9	2.5-4	15.8	17.9	3.45-25.92
Centre 10	5	6.27	7.2	
Total		7.89	9.5	

TABLE 2 Total number and % of antineoplastic preparations with deviations >10% and >20% (excluding preparations with wider extended tolerances)

	>10% (N)	>10% (%)	>20% (N)	>20% (%)
Centre 1	1241	3.84	410	1.27
Centre 2	477	2.37	136	0.67
Centre 3	76	0.49	33	0.21
Centre 4	941	2.08	247	0.53
Centre 5	849	1.90	429	0.96
Centre 6	322	1.66	94	0.48
Centre 7	1972	5.04	430	1.10
Centre 8	247	1.41	77	0.44
Centre 9	463	2.23	188	0.90
Centre 10	7243	1.44	2424	0.48
Mean	13 831	2.25	4467	0.71

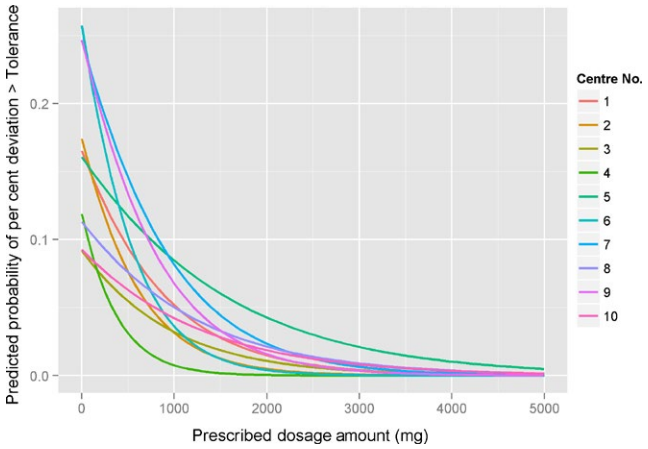

FIGURE 3 Predicted probability of preparation out of tolerance vs. prescribed dosage amount

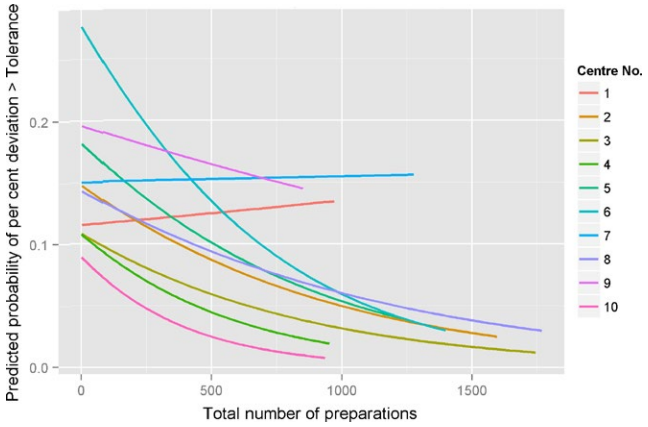

FIGURE 4 Predicted probability of preparation out of tolerance vs. total number of preparations per centre

dosing errors tended to be lower for drugs prepared more often (Figure 4).

Table 3 presents data for individual antineoplastic drugs prepared in the study with OOT error rates >10%. The highest error rates occurred with teniposide (59.26%) and alemtuzumab (55.89%) although prescribing levels of these agents were low. Among the most commonly prepared medications, OTT rates were highest for bortezomib (35.4%) and vincristine (32.36%).

4 | DISCUSSION

This analysis showed that 7.89% of 759 060 doses of antineoplastic drugs prepared across the 10 study centres had error levels outside the accepted tolerance range set by each centre; it is highly likely these errors would have gone undetected using traditional volumetric preparation. When this figure was adjusted to equally weigh the centres and their extent of service provision for preparation of antineoplastic agents, the mean OOT rate was 10.44%.

TABLE 3 Out-of-tolerance rates (N and %) and total preparations (N) for drugs with highest out-of-tolerance rates (only drugs with out-of tolerance rates >10% are shown)

International drug name	OOT (N)	Total	Percentage
Teniposide	16	27	59.26
Alemtuzumab	147	263	55.89
Blinatumomab	7	14	50
Methotrexate	1274	3352	38.01
Cabazitaxel	167	464	35.99
Bortezomib	5414	15 295	35.4
Dactinomycin	34	99	34.34
Fludarabine	1284	3880	33.09
Vincristine	2580	7973	32.36
Pegaspargase	16	50	32
Asparaginase	37	147	25.17
Topotecan	2189	8969	24.41
Decitabine	92	387	23.77
Pertuzumab	629	2992	21.02
Azacitidine	6019	28 736	20.95
Cytarabine	2479	12 346	20.08
Paclitaxel formulated as albumin-bound nanoparticles	125	625	20
Pembrolizumab	25	126	19.84
Vindesine	18	99	18.18
Aflibercept	179	1007	17.78
Arsenic Trioxide	78	454	17.18
Catumaxomab	1	6	16.67
Melphalan	157	1032	15.21
Eribulin	26	172	15.12
Thiotepa	8	53	15.09
Raltitrexed	3	20	15
Docetaxel	3571	25 375	14.07
Mitomycin C	238	1709	13.93
Obinutuzumab	6	44	13.64
Cladribine	111	829	13.39
Brentuximab Vedotin	14	105	13.33
Trastuzumab Emtansine	138	1211	11.4
Busulfan	268	2430	11.03
Bleomycin	223	2065	10.8
Etoposide	2603	25 589	10.17
Pixantrone	6	60	10

OOT, out of tolerance.

The overall error level seen with antineoplastic drugs was consistent with that seen for all preparations in the study (antineoplastic and non-antineoplastic, n=1 199 400, OOT 9%), and trends for different centres were also similar.

To our knowledge, this is the first large-scale retrospective research that analysed data from real-time log files which record all events during the preparation process for IV antineoplastic drugs. This made it possible to apply statistical methods to describe relationships and deviations which occurred and identify medication errors which would otherwise have gone unrecognized.

The OOT error level in our study is in accordance with the 7% error rate identified in 15 843 IV drug doses prepared in a single oncology ambulatory care pharmacy in the USA;[6] 71% of these were detected gravimetrically. At the same pharmacy, 51 037 chemotherapy doses prepared without using the gravimetric workflow software system had a self-reported error rate of just 0.096% (74-fold less than with automated gravimetric software system).

All errors in our multicentre study and in the single-centre US study were detected during the preparation process and did not need to be corrected post-production. In the US study, this resulted in reductions of 34% of technician production time and 37% of pharmacist checking time.

Although the overall OOT error rate in our study was 7.89%, five centres had levels >10%, the highest being >16%. Centres with the highest overall error rates also tended to have higher rates of "not at first attempt" errors and of errors >10% and >20% OOT.

Logistic regression identified significant relationships between OOT error rates and other recorded variables, including between OOT error rates and each drug's total number of preparations ($P<.005$). With few exceptions among centres, the more often an individual drug was prescribed, the less likely that an OOT dosing error was made (Figure 4). The probability of a preparation being outside tolerance generally fell rapidly as the number of drug preparations increased over 500 preparations (measured during the first 10 000 preparations). A continuing decline in error rate was recorded at centres with highest preparation levels for individual drugs, reaching very low levels at centres preparing individual drugs ≥1500 times. The reduction in dosing errors was significant ($P<.05$) for all centres except two (centre 1 $P=.13$ and centre 7 $P=.62$) and is likely to have reflected increased experience with preparation methodology.

How important are medication errors that are >10% and >20% of target dose? Regulatory authorities such as the European Medicines Agency (EMA) require that, to show bioequivalence, 90% confidence interval of the ratio of the area under the curve (AUC) for two drugs must fall within the range of 80% to 125%.[2,7] For drugs with a narrow TI, the EMA recommends the range be 90% to 111.11%. It is therefore reasonable to suggest that medication deviations from 80% to 125% for most drugs and 90% to 111.11% for those with a narrow TI—as is the case for many antineoplastic agents—can be considered problematic.

Accepted stability levels for drug preparations also provide useful insights about appropriate tolerance levels for medication errors. Pharmaceutical scientists commonly regard a stability limit of 90% as acceptable.[8] However, recent European guidance on practical stability studies of anticancer drugs draws attention to the need to consider TI, variability in pharmacokinetic/pharmacodynamics (PK/PD) and

specific clinical use, and risks related to degradation of products. The guidance suggested that the classical limit of 10% of degradation may be inappropriate in some cases.[9]

The narrow TI of anticancer drugs requires exact dosing to obtain sufficient pharmacological activity and minimize toxicity. Further, clinical effectiveness of antineoplastic regimens is complicated by interpatient variability, genetic polymorphisms in drug-metabolizing enzymes and drug-drug interactions caused by polymedication.[10]

Whereas clinical factors are difficult to control, the variability of pharmacological factors may be lessened by introducing sophisticated methods that reduce the error margin in the preparation of antineoplastic agents. In our study, we found that the volumetric preparation method is unable to sufficiently detect the compounding variability that causes preparation errors. A preparation error threshold of 10% was chosen for our evaluation, based on previously published studies[11,12] and the Société Française de Pharmacie Oncologique (SFPO)/European Society of Oncology Pharmacy (ESOP) guidelines[9] used in European countries. The German Pharmacopoeia DAB 10 already states in its monograph "V.5.2 Uniformity of single dose drugs" that for parenteral drugs, dosing deviation must stay within ±10% and ±15% for doses >40 and <40 mg, respectively.[13] This monograph has been replaced by the European Pharmacopoeia general chapters on uniformity of mass of single-dose preparations (2.9.5), uniformity of content of single-dose preparations (2.9.6) and uniformity of dosage units (2.9.40) with a more sophisticated statistical approach.[14]

Other sources[15,16] allow a variation of only 5%, based on volumetric preparation processes. However, the results of this study demonstrate that the final doses checked by gravimetric measurement are often in a range that can be very much higher than the assumed 5%.

With these factors in mind, oncology pharmacists may also need to take such parameters into account when deciding appropriate error tolerance levels for different antineoplastic agents.

Our study demonstrated a mean rate of deviations >10% of 2.25% (range 0.49% to 5.04% across sites) and a mean average rate of deviations >20% of 0.71% (range 0.21% to 1.27% across sites), after excluding preparations with extended tolerances >10% and >20%, respectively. This suggests data retrieved from the gravimetric workflow system verified nearly 13 831 doses of antineoplastic agents that could have been administered to patients at levels which may have had a negative impact on therapeutic outcome.

Possible therapeutic impact gains associated with the use of the gravimetric approach need to be considered within the context of the tolerance settings applied by system administrators. Standard preparation tolerances set by centres fell within a relatively narrow range (2.5% to 6%) with extended preparation tolerances showing much wider variation (3.1% to 30%).

The extended range applies to drugs whose formulation makes it very difficult to stay within normal limits for preparation, and generally applies to drugs requiring low volumes/masses (eg <2000 mg). The lower the solution mass, the higher the tolerance. The high extended tolerances used at some centres indicate that it may be difficult to achieve adequate dosing accuracy for some drugs. However, the variation in extended tolerances for some drugs, reported across centres, merits further investigation.

The challenge of minimizing dosing errors when working with very small amounts of drug is clearly demonstrated in our study (Figure 3). The probability of preparations being OOT fell rapidly as prescribed dosages increased up to 1000 mg and were almost zero at most centres when doses of ≥3000 mg were prepared. One explanation could be that drugs prepared at higher volumes contain more active ingredient and require larger amounts of diluent during preparation. These high-volume formulations are therefore less likely to result in withdrawal of an incorrect dose compared with low-volume drugs, such as bortezomib (see extended tolerances above).

Tolerance levels set by centres in our study were particularly exceeded for certain drugs. For example, nearly 60% of teniposide preparations and over half of those of alemtuzumab were OOT (Table 3). Neither drug was commonly prescribed, so it might be considered that the high error rates were in line with another finding from the study that the less often an individual drug was prescribed, the more likely an OOT dosing error was to occur. However, as error rates were also high for some other more commonly prescribed medicines, such as bortezomib, unfamiliarity with preparation cannot be the only reason for OOT variations for different drugs. As different centres used different technical equipment for preparing drugs, this may have influenced variability for different medicines, but the contribution to possible negative outcomes needs to be further investigated.

Our findings are relevant both to centres that have already implemented a gravimetric measurement system and to those still using traditional volumetric systems for preparing antineoplastic drugs, which may not achieve effective recognition of medication errors.

Possible limitations of our research include a lack of information about devices used during the preparation process and how these may impact on occurrence of medication errors. Variation between participating centres in use of needles, chemospikes and safety devices aimed at reducing contamination due to aerosol generation may affect risk of medication errors.

As this was a retrospective study, we were unable to ensure standardization of preset error tolerance levels. The 3.5% difference in preparation tolerance between centres may have affected the variation in number of first withdrawals that are out of tolerance, but was not far from the aimed 2% difference.

Standardized density values for different antineoplastic drugs used in the study were stored in the database of the gravimetric software. However, as there may have been small variations in density between drug batches (it is not common practice for manufacturers to provide values with each batch), different centres may have used slightly different density values stored in their database at different times and this may have increased variations. Even so, as the maximum tolerance

set by any centre did not exceed 6%, this remains well below the 10% threshold for bioequivalence that the EMA considers relevant for drugs with a narrow TI.

Use of different antineoplastic agents varied across the centres in the study. Hence, the contribution of some centres to error rates with certain drugs may have been disproportional.

5 | WHAT IS NEW AND CONCLUSION

The evaluation of data from 10 centres in five European countries has shown that the introduction of a gravimetric preparation system for antineoplastic agents can detect and prevent medication errors which would not have been recognized by traditional methods. These may have caused serious toxicity or underdosing, potentially resulting in suboptimal outcomes for patients undergoing anticancer treatment.

Using logged data during gravimetric preparation of drugs, it was possible to identify the previously unreported dimension and potential impact of volume errors during medication preparation. At the same time, it was possible to show that a gravimetric IV workflow software system is capable of largely eliminating this kind of potentially life-threatening medication error.

The demonstration that some antineoplastic drugs are more prone to volume errors than others, and that errors are particularly common when prescribed dosages are lowest, should inform research into future improvements in formulations.

European guidance already supports the use of the computer-assisted gravimetric approach for preparation of individualized ready-to-use cytostatic solutions,[4] and obligatory implementation of gravimetric methodology for medication preparation is overdue.

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CONTRIBUTORS

RT was responsible for the design of the study. All the authors have read and approved the final version of the manuscript. RT drafted the manuscript, and JB contributed with statistical advice and conducted the statistical analyses. MC contributed to manuscript revision. RT had the main responsibility for the conception and design of the study and revisions of the manuscript drafts.

ETHICAL APPROVAL

No patient data were collected; the study was therefore deemed exempt from ethics review by classification as an improvement activity and not human subject research.

ADMINISTRATIVE APPROVAL

Written permissions for data extraction from the centre databases were retrieved from (hospital) administrators, pharmacy directors and medical directors.

PRIVACY POLICY

The Austrian Society of Oncology Pharmacy (ASOP) provided a declaration about which data will be extracted for the study and how these data will be used.

Only centres with a valid privacy policy declaration mutually signed between BD Cato™ and a representative of the organization were responsible for participating centres that were eligible for data extraction performed by BD Cato™ IT specialists.

CONFLICT OF INTEREST

The authors have declared no conflict of interests.

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